REMARKS

The Official Action of January 17, 2007, and the prior art relied upon therein have been carefully reviewed. The claims in the application are now claims 1 and 3-17, including presently withdrawn claims 10-13. Applicants respectfully maintain that their claims define novel and unobvious subject matter and therefore should be allowed. Accordingly, the applicants respectfully request favorable reconsideration and allowance.

Acknowledgement by the PTO of the receipt of applicants' papers filed under Section 119 is noted.

The restriction requirement has been repeated and made final, whereby claims 10-13 have been withdrawn from further consideration. Applicants do not understand why claim 13 has been withdrawn, as it is directed to the product. Of course, claim 13 is a hybrid product-by-process claim, but the bulk of the claim is directed to the structure of the product, similar to claim 1, whereby claim 13 should certainly be included among the elected claims, particularly bearing in mind that the PTO will seldom give any weight to the process features of a product-by-process claim.

Applicants continue to respectfully maintain that claim 13 is in any event a linking claim.

Claims 1, 3, 5-9, 14 and 15 have been rejected under Section 102(e) as being anticipated by Iida et al USP 6,893,658 ("Iida"). This rejection is respectfully traversed.

Claim 2 has not been rejected as anticipated by Iida. Claim 2 has now been incorporated into claim 1, whereby claim 1 as amended corresponds with original claim 2.

Accordingly, applicants need not address the rejection of claim 1 at the present time in view of the aforementioned amendment incorporating claim 2 into claim 1.

As claims 3, 5-9, 14 and 15 depend from and incorporate the subject matter of claim 1, the rejection also need not be addressed at this time with respect to such dependent claims.

Claims 1-9, 14 and 15 have been rejected under Section 103 as obvious from Iida[1]. This rejection is respectfully traversed.

The light-stabilized soft capsule shell of the present invention contains a high amount of a non-water-soluble light-shielding agent, namely 5-30 wt% based on the total amount of all components constituting the shell. This is not an arbitrary amount, but is critical to the present invention such as pointed out in the paragraph spanning pages 3 and 4 of applicants' specification.

> As a result of extensive and intensive efforts directed to recipes for capsule shell of soft capsule formulations and methods for their manufacture, the inventors of the present invention have developed a recipe for capsule shell including a high content of a non-water-soluble light-shielding agent … . They also have found that this … allows a sufficient reduction in light transmittance even for soft capsule shells less than 200 μm in thickness, thus enabling light stabilization of soft capsule formulations containing a light-unstable medicament even with a smaller capsule size.

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[1] Respectfully, the rejections of claims 1, 3, 5-9, 14 and 15 as both anticipated by Iida and obvious from Iida appear to be inconsistent, as it is not seen how it is possible for a claim to be both anticipated by and obvious from the same citation.

As described in this paragraph, the high content of a non-water-soluble light-shielding agent allows a sufficient reduction in light transmittance even for soft capsule shells less than 200 μm in thickness, thus enabling light stabilization of soft capsule formulations containing a light-unstable medicament even with a smaller capsule size.

That the range is critical is confirmed by the test examples in applicants' specification, and particularly Example 2, the results of which are illustrated in Fig. 4. As claimed, the minimum content of non-water-soluble light-shielding agent is 5%, and Fig. 4 shows that with only 4%, the results were relatively poor. Also see applicants' specification in the paragraph spanning pages 19 and 20 (this paragraph also provides support for new claims 16 and 17, which claims are patentable for the same reasons as the other claims as pointed out herein).

The PTO relies on Iida which teaches the use of white pigment, e.g. titanium oxide, to protect the medicament within the capsule from light and heat, but wherein the amount of such pigment is **very low** compared with what is claimed. Thus, at column 3, lines 21-23, Iida states:

> It [the amount of white pigment used] is preferably 1.5% by weight or less, particularly 1.0% by weight or less, of the total amount of capsule shell components.

There is not the remotest hint to one of ordinary skill in the art to increase the quantity of shielding agent to such a significantly greater degree than what is taught by Iida. Such a teaching comes only from applicants' own specification, which was not available to the person of ordinary skill in the art at the time the present invention was made. Applicants

respectfully submit that it is not fair and not proper to use an applicants' own specification as a teaching to modify the prior art in a way which the prior art itself does not teach, and this is moreover contrary to MPEP 2143..

The PTO relies upon *In re Aller,* 105 USPQ 233, 235 (CCPA 1955) to urge that applicants' selection of a vastly greater amount of shielding agent than taught in the prior art would have been obvious due to routine experimentation, but this is not so. Whereas the PTO deems the claimed quantity of shielding agent to be a mere optimum, this is in fact the required range necessary to achieve the required degree of shielding. In *Aller,* the court held that when the general conditions of a claim are disclosed in the prior art, in that case a temperature range, it is not inventive to discover optimum or workable ranges by routine experimentation. But *Aller* also makes clear that "Changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art" [citation omitted; 105 USPQ at 235]. See also *In re Antonie,* 195 USPQ 6 (CCPA 1977), where the rejection was reversed. Applicants have indeed produced a new and unexpected result which is different in kind, as demonstrated in Fig. 4 where even 4% of the shielding agent was insufficient, such 4% being several times the amount suggested in the relied upon prior art.

Moreover, please see *In re Yates,* 211 USPQ 1149 (CCPA 1981), where the holding in *Aller* was explained and the rejection was reversed. *Yates* involved claims for a process for oxidizing an olefin to an unsaturated aldehyde. The claim specified that a gaseous mixture of olefin and molecular oxygen is combined with a catalyst of specified composition at

an elevated temperature to convert from 25 to 80% of the olefin to product, maintaining the unsaturated acid content of the product at less than 2% of the unsaturated aldehyde content. The prior art, Okada, disclosed a process for catalytically oxidizing olefins to unsaturated aldehydes and acids, which generally paralleled the *Yates* process. However, Okada did not disclose the ratio of acid to aldehyde produced, nor did it disclose the relation of the degree of conversion to percentage production of acids or exemplify processing having a degree of conversion greater than 80%.

Okada showed examples of olefin to aldehyde oxidation reactions using various oxidation catalysts similar to those used by Yates. In the examples, the percentage of acid was generally in the 3-10% range, and there was no clear relationship between conversion and acid production. The court concluded that the examples, taken as a whole, supported the argument that a person of ordinary skill in the art would not have expected the degree of olefin conversion to be result effective for the percentage production of unsaturated acid (211 USPQ at 1151).

As in *Yates*, the prior art presently relied upon does not lead the person of ordinary skill in the art to either vastly increased amounts of shielding agent used, or the vastly improved results achieved thereby.

Moreover, applicants are aware of extrinsic evidence which teaches that the content of a non-water water-soluble light-shielding agent, e.g. titanium dioxide, in a soft capsule shell **should not exceed 1%.** Thus, attached hereto is a copy of a article in the name of Matsuda et al, *Chem. Pharm. Bull.*, 28(9), 2665-2671, 1980, which contains such a teaching, noting especially the last paragraph on page 2669, which

clearly says that "the effect of concentration seems to level off somewhat above 1% addition, … ."

Also see Fig. 2 at page 2667, exhibiting changes in light transmittance of gelatin films having 80 μm of thickness observed within a wavelength of 290-410 nm, when varying the content of titanium oxide (0, 0.5, 1.0, and 1.5 wt%) in the gelatin films; and Fig. 4 at page 2667 of the document, exhibiting changes in average light transmittance of gelatin films having 50-150 μm of thickness observed within a wavelength of 290-450 nm, when varying the content of titanium oxide (0, 0.5, 1.0, and 1.5 wt) in the gelatin films.

Both figures show that light transmittance of gelatin films decreases as the titanium oxide content increases. **However, these figures also show that a degree of the decrease in the light transmittance becomes smaller as the titanium oxide content increases.** This will be apparent when comparing distances between light transmittance curves in the figures for 0 wt% and 0.5wt%, for 0.5 wt% and 1.0 wt%, and for 1.0 wt% and 1.5 wt% of the titanium oxide content. The distance between the curves for 1.0 wt% and 1.5 wt% is particularly very short. Thus, Matsuda et al conclude in the abstract that **"the effect of concentration seemed to disappear above 1% addition"**. This document is part of the prior art "as a whole".

Therefore, the skilled worker in the art would not have been motivated by the disclosure of this document to make a soft capsule having a shell of 80 μm (this value also means 200 μm or less, which is recited in claim 1 of the present application) in thickness, which contains titanium dioxide in an amount of 1 wt% or more of the weight of the shell, let alone more than 5 wt%.

Contrary to the teaching of Matsuda et al and Iida et al, the present inventors found that the light shielding effect resulting from increase in the content of titanium dioxide does not reach a plateau even when the content exceeds 1 wt%. This finding is specifically supported by working examples in the present specification. Especially, Fig. 4 shows that, even in the range of 4% to 20% titanium oxide content, which is higher than 1%, there is not any minimum limit for light remittance, but that the light-shielding effect is enhanced as the titanium oxide content becomes higher. The present invention is based on this new finding. Iida neither describes nor teaches this finding. Therefore, the present invention having a feature that 5-30 wt% of a non-water-soluble light-shielding agent is contained in a shell would not have been obvious from Iida.

Also, it should be noted that it was difficult to produce a soft capsule shell having a high content of a non-water-soluble light-shielding agent, e.g., titanium oxide, with a practical satisfactory quality. Specifically, as described in pages 24-25 of the present specification, to reduce deviations in the light-shielding effect of the shell among soft capsule formulations, it is necessary to keep uniform dispersion of a non-water-soluble light-shielding agent in a shell-forming solution from the beginning to the end of encapsulation. However, when preparing a soft capsule shell having a high content of a non-water-soluble light-shielding agent, it was difficult to maintain successful dispersion of the agent, even when the agent was added to a solution of a gelling agent (e.g. gelatin) and then treated by ultrasonication.

This problem was a barrier to production of a soft capsule shell having a high content of titanium oxide, with a

practically satisfactory quality. To resolve this problem, the present inventors utilized a method of dispersing a non-water-soluble light-shielding agent in water by ultrasonication before being added to a solution of a gelling agent, instead of adding a water suspension of titanium dioxide to a solution of a gelling agent before ultrasonication. In other words, ultrasonication is conducted in a middle step of preparing the solution for the soft capsule shell, not in the last step. This fact should be considered when evaluating the unobviousness of the present invention.

Withdrawal of the rejection is in order and is respectfully requested.

The prior art documents of record and not relied upon by the PTO have been noted, along with the implication that such documents are deemed by the PTO to be insufficiently material to warrant their application against any of applicants' claims.

Applicants believe that all issues raised in the Official Action have been addressed above in a manner that should lead to patentability of the present application. Favorable consideration and early formal allowance are respectfully requested.

Respectfully submitted,
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Chem. Pharm. Bull.
28(9)2665—2671(1980)

Photostability of Indomethacin in Model Gelatin Capsules: Effects of Film Thickness and Concentration of Titanium Dioxide on the Coloration and Photolytic Degradation[1)]

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The dependence of the photostability of indomethacin on the capsule shell thickness and on the concentration of titanium dioxide used as an opacificient was investigated using gelatin films prepared by casting as models of hard gelatin capsules. The film thickness and concentration of opacificient were varied in the ranges of 50—150 μm and 0—1.5% of the amount of dried films, respectively. Films and indomethacin tablets were exposed to a 400 W mercury vapor lamp for 120 min, then coloration of the enclosed indomethacin was measured by tristimulus colorimetry, and evaluated as Hunter's color difference. The chemical stability of the drug was determined by following the ultraviolet spectrophotometric change of a solid sample.

There was a good linear relationship between color difference values and the square root of exposure time at all concentrations and thicknesses. The coloration rate constants calculated from the slopes of these lines were affected by both parameters, and decreased significantly as the film thickness was increased at every concentration of opacificient. However, the effect of concentration seemed to disappear above 1% addition. The coloration rate was directly dependent on the average transmittance of films over the wavelength range relating to the photostability of indomethacin.

Degradation of indomethacin followed apparently sequential first-order kinetics. Apparent conversions after 120-min exposure as determined from the UV spectra were also affected by both parameters and were below 3% at thicknesses above 80 μm at every opacificient concentration tested; this represents excellent protection of indomethacin.

Keywords——indomethacin; gelatin capsule; gelatin film; photostability; photostabilization; effect of film thickness; effect of opacificient; coloration; photolytic degradation; solid dosage form

Many pharmaceutical products require light-resistant containers to protect them from photochemical deterioration. In most instances, a container made of good quality amber glass will reduce the light transmission sufficiently, and may protect light-sensitive pharmaceuticals. Hard gelatin capsules are solid dosage forms which may be considered as "primary" containers. For better protection against light, the formulations of capsule shells should therefore be considered from the viewpoint of light transmission. Titanium dioxide has been widely used in these formulations as an opacificient. Although this filler material has been recognized to modify the moisture permeability of polymer films,[3,4)] very little information actually exists concerning its opacificient role.

In the present study, titanium dioxide was incorporated into gelatin films, and the effect of the light transmission properties of the films on the coloration and photolytic degradation of indomethacin protected by these films was investigated under ultraviolet irradiation.

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1) This paper forms Part VII of "Stability of Solid Dosage Forms." Part VI: Y. Matsuda, K. Kouzuki, M. Tanaka, Y. Tanaka, and J. Tanigaki, *Yakugaku Zasshi*, 99, 907 (1979).
2) Location: *Motoyama-Kitamachi, Higashinada, Kobe 658, Japan.*
3) J.W. Parker, G.E. Peck, and G.S. Banker, *J. Pharm. Sci.*, 63, 119 (1974).
4) K. Bayer, M. Soliva, and P. Speiser, *Pharm. Ind.*, 34, 677 (1972).

Experimental

Preparation of Indomethacin Tablets——Indomethacin JP (below 200 mesh) was compressed into 0.5 g flat-faced tablets, 15 mm in diameter, as models of the enclosed active ingredient, using a compression-tension testing machine. In order to obtain reproducible changes in the surface color of these tablets in subsequent experiments, a constant compression force of 200 kg was used. Samples were stored over silica gel in a desiccator in the dark until used.

Preparation of Gelatin Films——As described in the previous study,[1] titanium dioxide was added to molten gelatin aqueous solution and dispersed thoroughly using a homogenizer. The concentrations used were 0.5, 1.0, and 1.5 w/w% of the amount of dried films. Solutions were poured onto horizontal flat polyvinyl chloride plates. Rings made of the same material, with a diameter of 5 cm, were used to control the area of spreading and the thickness of films. The solvent was allowed to evaporate for 15 hr at constant temperature and humidity (25°, 50±2% R.H.). Dried films were peeled from the plate and sample films of 3×3 cm were cut off.

The thickness of films was varied from 50 to 150 μm; it was calculated as the mean of the measured values at five fixed points on a film using an electromagnetic thickness meter (Permascope type ES-8, Helmut Hischer GMBH, West Germany). These films were fixed on the front of the holders for sample tablets reported previously,[5] as models of capsule dosage forms.

Ultraviolet Irradiation——For kinetic studies, a sample film and tablet were exposed to UV irradiation in a fading tester with a 400 W mercury vapor lamp, as reported previously,[1,5-7] and subjected to colorimetric measurement at appropriate intervals. A grating monochromator[8] (model CRM-50, Japan Spectroscopic Co., Tokyo) with a 5 kW xenon lamp adjustable for wavelength in the range of 295—475 nm was also employed to obtain spectra for coloration and photolytic degradation of unprotected indomethacin. A bandwidth of 5 nm was used at all wavelengths for irradiation.

Colorimetric Measurements——The surface color of the tablets was measured using a color and color difference meter.[8] After each exposure, Hunter's color difference, ΔE,[9] was calculated from three colorimetric values to evaluate the degree of coloration.

Absorption Measurements——Transmittance curves of films and ultraviolet absorption spectra of indomethacin in the solid state were recorded by the method described previously.[7] The average transmittance of the film, as discussed below, was obtained by calculating the area under the transmittance curve in related wavelength ranges.

Results and Discussion

Photosensitivity of Indomethacin

Indomethacin is photosensitive[10a] and becomes colored on exposure to light,[10b] and photodegradation has been reported in aqueous solution under UV light.[11] However, there are no data on the effect of light on solid-state indomethacin. Therefore, we required fundamental data on its photosensitivity before beginning the encapsulation studies.

Figure 1 shows action spectra for coloration and photolytic degradation under a fixed irradiation energy of 3.82×10^8 erg/cm^2. In this graph the degree of photolytic degradation was evaluated in terms of apparent conversion, as discussed later; it was defined as the ratio of absorption intensity at 270 nm after to that before irradiation in the UV absorption spectrum. Within the wavelength range observed and under normal storage conditions for drugs, the action spectrum for coloration exhibited a characteristic band which showed the greatest effectiveness at around 372 nm. In the region above 372 nm, ΔE decreased rapidly, but coloration still remained appreciable above 400 nm. The pattern of the action spectrum for photolytic degradation was in good accord with that for coloration. Based on these

5) Y. Matsuda, H. Inouye, and R. Nakanishi, *J. Pharm. Sci.*, 67, 196 (1978).
6) Y. Matsuda and Y. Minamida, *Yakugaku Zasshi*, 96, 425 (1976).
7) *Idem, Chem. Pharm. Bull.*, 24, 2229 (1976).
8) Y. Matsuda and M. Itoh, *Asian J. Pharm. Sci.*, 1, 107 (1979).
9) R.S. Hunter, *J. Opt. Soc. Am.*, 38, 661 (1948).
10) *a*) "The United States Pharmacopeia," XX, Mack Publishing Company, Easton, PA., 1980, p. 399; *b*) "The Pharmacopeia of Japan," IX, Yakuji Nippo Ltd., Tokyo, 1975, p. 281.
11) *a*) E. Pawelczyk, B. Knitter, and K. Knitter, *Pharmazie*, 32, 483 (1977); *b*) E. Pawelczyk and B. Knitter, *ibid.*, 32, 698 (1977).

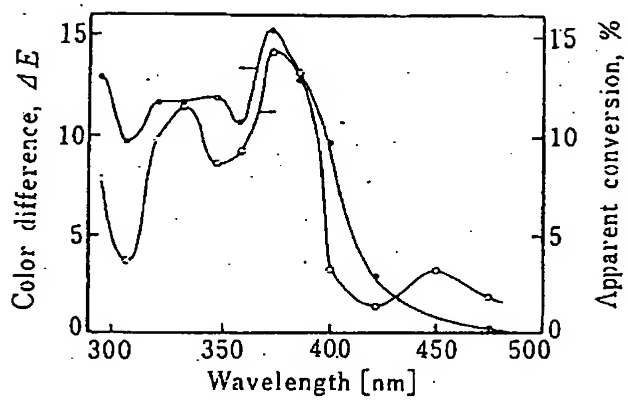

Fig. 1. Action Spectra for Coloration and Photolytic Degradation of Indomethacin

○, apparent conversion; ●, color difference.

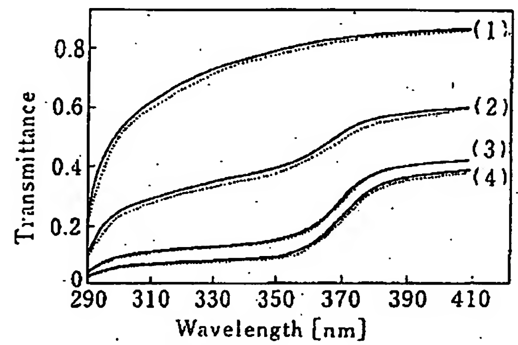

Fig. 2. Effect of Ultraviolet Irradiation on the Transmittance Curves of Gelatin Films

Film thickness: 80 μm. Numbers (1)—(4) in the figure represent the concentrations of opacificient, 0, 0.5, 1.0, and 1.5%, respectively.
——: before exposure;
------: after 120-min exposure.

results, it can be deduced that the action of lower wavelengths in the visible region should not be neglected in assessing the photosensitivity of indomethacin.

Light Transmission Properties of Gelatin Films

If the transmittance of gelatin films is changed by exposure to light, it would be difficult to determine the protection provided by these films. Figure 2 shows the effect of UV irradiation on the transmittance curves of gelatin films having a thickness of 80 μm after 120-min exposure. The light transmission properties of film without opacificient were not affected much even under severe exposure conditions. It is evident that the film without opacificient exhibits a rather high transmittance in the ultraviolet region below 400 nm. Such transmittance was greatly reduced, especially below 350 nm, with increasing concentration of opacificient. The transmittance curves were hardly affected, even by 120-min exposure, at any concentration of opacificient. Thus gelatin films can be considered photostable as regards light transmission properties.

The effects of film thickness and concentration of opacificient over the whole range investigated on the light transmission properties of films are summarized in Fig. 3, in which the cut wavelength, λ_{T50}, denotes the 50% transmission point on the transmittance curve,

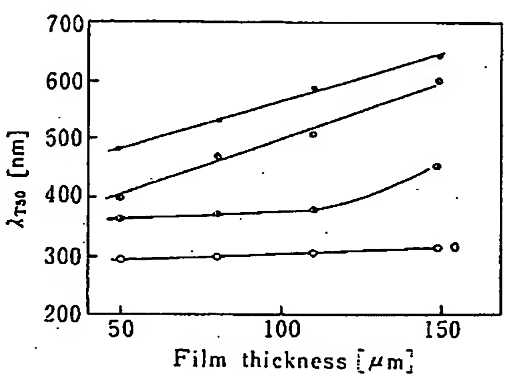

Fig. 3. Effect of Film Thickness on the Cut Wavelength of Films, λ_{T50}

Concentration of opacificient:
○, 0%; ◑, 0.5%; ◐, 1.0%; ●, 1.5%.

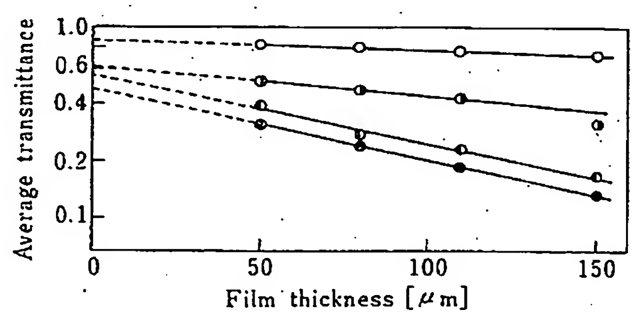

Fig. 4. Semi-logarithmic Plots of Average Transmittance of Films against Film Thickness

Concentration of opacificient:
○, 0%; ◑, 0.5%; ◐, 1.0%; ●, 1.5%.

The λ_{T50} values of films without opacificient were not significantly affected by film thickness, indicating poor protective effectiveness against UV light. In contrast, at any concentration of opacificient, changes in the value of λ_{T50} were proportional to film thickness, and the higher the concentration, the more satisfactory was the shielding effect. Referring to the results shown in Fig. 2, it would be expected that film formulations giving λ_{T50} values of more than 450 nm would show desirable protective effectiveness. However, to evaluate the protective effectiveness more precisely, determination of the average transmittance over the wavelength range where indomethacin is photosensitive would be preferable to λ_{T50}.

The values of average transmittance between 290 and 450 nm are plotted in relation to the film thickness in Fig. 4. As is clear from Fig. 4, it decreases with the increase of either film thickness or concentration of opacificient. It appears that both parameters are directly and linearly related on a semi-log scale over the whole range of film thickness used. This relationship indicates that the following equation[12] can be applied to a semi-transparent material such as that used in the present work.

$$T=(1-R)^2\exp(-\alpha x),\quad R=\left(\frac{n-1}{n+1}\right)^2 \qquad \text{(Eq. 1)}$$

where, T: average transmittance
R: reflectance
x: film thickness
α: apparent extinction coefficient
n: refractive index of film

Reflectance and apparent extinction coefficient calculated from Eq. 1, using the slope and the extrapolated value at zero thickness (Fig. 4), are plotted in Fig. 5. The reflectance value of about 0.062 for the film without opacificient was approximately equal to that of the plate glass (R=0.042)[13] having a refractive index of 1.52. The reflectance increased monoto-

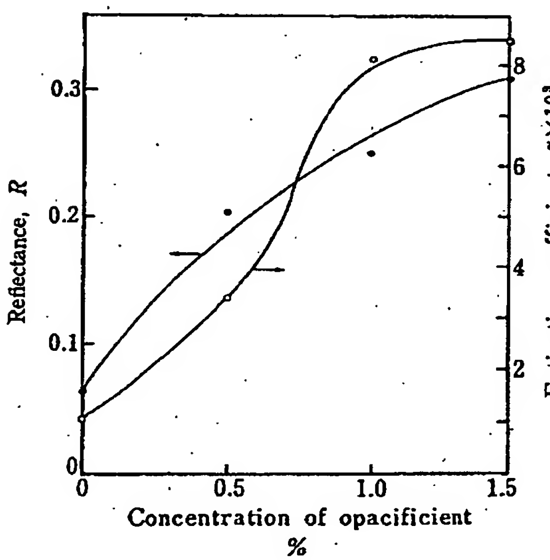

Fig. 5. Dependency of the Reflectance and Apparent Extinction Coefficient of Films on the Concentration of Opacificient

●, reflectance; ○, apparent extinction coefficient.

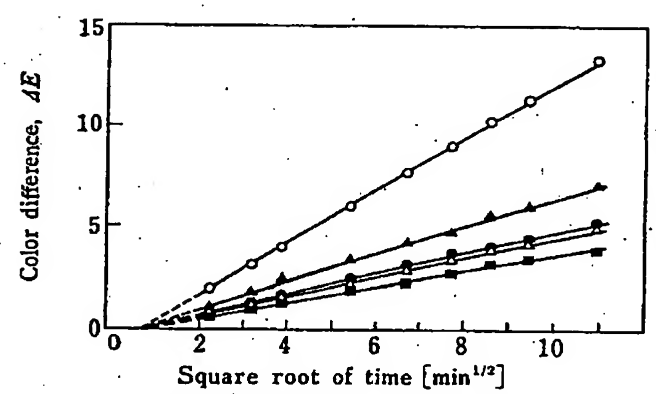

Fig. 6. Linear Plots of Color Difference as a Function of Square Root of Exposure Time

Concentration of opacificient: 1.5%.
○, without film; ▲, 50 μm; ●, 80 μm; △, 110 μm; ■, 150 μm.

12) S. Naruse, "Glass Engineering," Kyoritsu Publishing Co., Tokyo, 1966, p. 307.
13) K.A. Connors, G.L. Amidon, and L. Kennon, "Chemical Stability of Pharmaceuticals," John Willey and Sons Inc., New York, 1979, p. 90.

nously with increasing concentration of opacificient. On the other hand, the increase in apparent extinction coefficient seemed to level off somewhat above 1% addition. Since the coloration and photolytic degradation of an enclosed drug are affected only by the light transmitted through the capsule film, the results in Fig. 5 indicate that the combined effects of both reflectivity and absorptivity should result in good photostabilization in the higher concentration range.

Effects of Film Thickness and Concentration of Opacificient on Coloration

Figure 6 shows the effect of film thickness on the coloration of enclosed indomethacin for 1.5% addition of opacificient. Unprotected indomethacin showed more than 12 NBS units of color difference after 120-min exposure, which was quite clear visually.[14] Reduced coloration was observed with increasing film thickness, but even at 150 μm thickness, coloration was still nearly 4 NBS units, which is appreciable. The plots of color difference values against square root of exposure time, t, gave a good linear relation at all concentrations and thicknesses, and, therefore, equation 2 may be applied:

$$\Delta E = k(\sqrt{t} - 0.82) \qquad \text{(Eq. 2)}$$

where k is regarded as a coloration rate constant. The protective effectiveness can be evaluated in terms of k.

Figure 7 shows the effects of film thickness and concentration of opacificient on the coloration rate constant. A good linear relationship exists between the logarithmic value of rate constant and film thickness. The coloration rate constant fell significantly as the film thickness was increased at every concentration of opacificient, but the effect of concentration seemed to level off somewhat above 1% addition, as is evident in this figure. It is clear from this evidence and the results obtained in Fig. 5 that the coloration rate is affected more significantly by the absorptivity than by the reflectivity of the film. The graphical behavior of the coloration rate constant closely resembles that of the average transmittance in Fig. 4, suggesting a strong correlation between these parameters. The coloration rate constant is plotted against

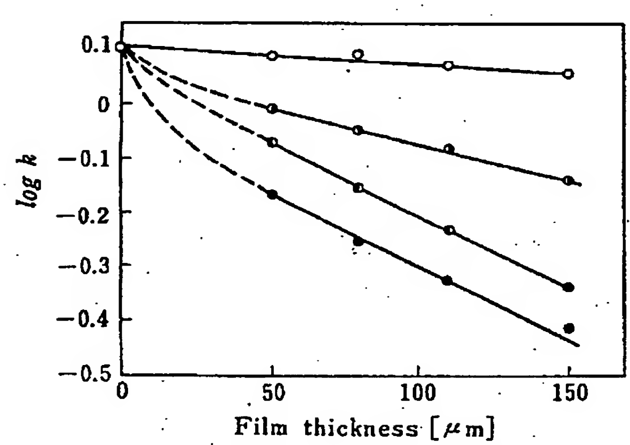

Fig. 7. Effect of Film Thickness on Logarithmic Coloration Rate Constant

Concentration of opacificient: ○, 0%; ◑, 0.5%; ◐, 1.0%; ●, 1.5%.

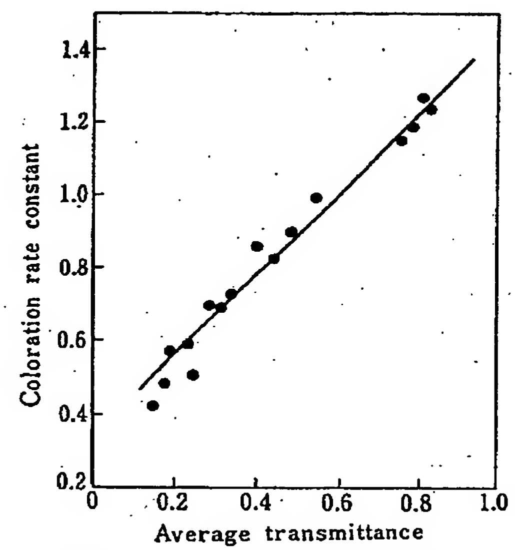

Fig. 8. Relationship between Coloration Rate Constant and Average Transmittance of Film

14) E.I. Stearms, *Am. Dyestuff Rep.*, 40, 563 (1951).

average transmittance in Fig. 8. There was a correlation coefficient of 0.988 ($n=16$, $p<0.001$), regardless of film thickness and concentration of opacificient, indicating that the coloration rate is directly controlled only by the average transmittance.

Photolytic Degradation

Photochemical degradation of indomethacin in phosphate buffer solution has been found to be a sequential reaction consisting of a series of zero-order processes;[11] there are three processes having different rate constants.

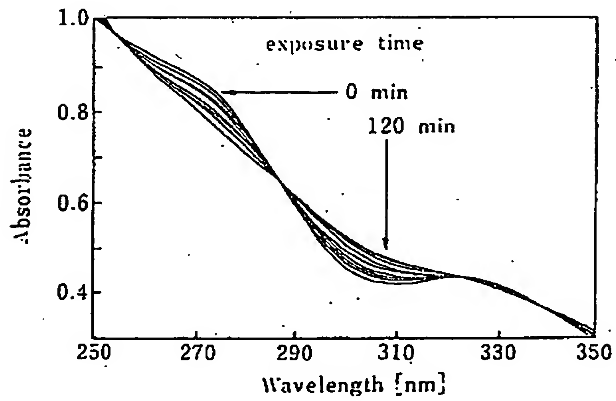

Fig. 9. Effect of Exposure Time on the Absorption Spectrum of Solid Indomethacin used as a Control

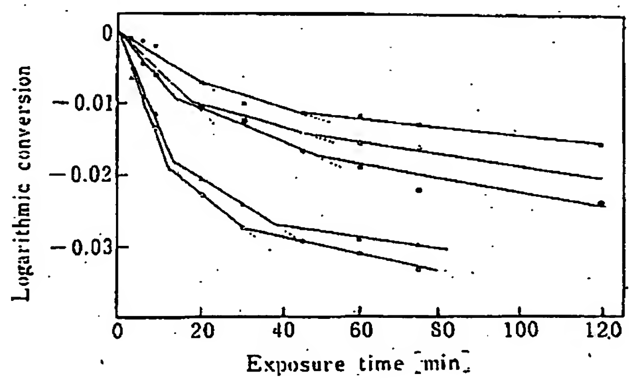

Fig. 10. Typical Apparent First-order Plots of Photolytic Degradation at Various Film Thicknesses

○, without film; ▲, 50 μ; ●, 80 μm; △, 110 μm; ■, 160 μm.

For the reason described in our previous report,[7] spectrophotometric analysis of indomethacin was done in the solid state, and a typical absorption spectrum for the control is shown in Fig. 9. In the original state before exposure, there was an absorption maximum and a minimum at 323 and 308 nm, respectively, with a weaker absorption band as a shoulder at 270 nm, which corresponds to the maximum absorption wavelength for the solution. As the exposure time increased, the absorption curve tended to flatten out, increasing the minimum and decreasing the maximum. Neither the maximum nor the minimum could be seen after 120-min exposure. The isosbestic points were at 254, 287, 322, and 339 nm. These points were observed for films showing higher average transmittance.

The ratio of absorbance after to that before exposure at 270 nm was taken as a measure of the apparent conversion, because the changes in absorption intensity were most marked at this wavelength. The values of these ratios are plotted against time in Fig. 10 for films without opacificient. The plots obtained were linear on the semi-log scale, indicating that the degradation of indomethacin in the solid state followed apparently sequential first-order kinetics in all the steps. Among the three degradation rate constants calculated from the slopes of individual lines, the rate constant of the first process was the greatest. It was about 3.4 times the rate constant of the second and 17.9 times that of the third process.

The effects of film thickness on these degradation rate constants are given in Fig. 11 in the form of the rate of stabilization (R_i), defined by the following equation 3:

$$R_i = \frac{k_{oi}-k_{li}}{k_{oi}} \times 100\ (\%) \qquad \text{(Eq. 3)}$$

where, k_{oi}: rate constant in the i th degradation process for the control

k_{li}: rate constant in the i th degradation process for the film having a thickness l

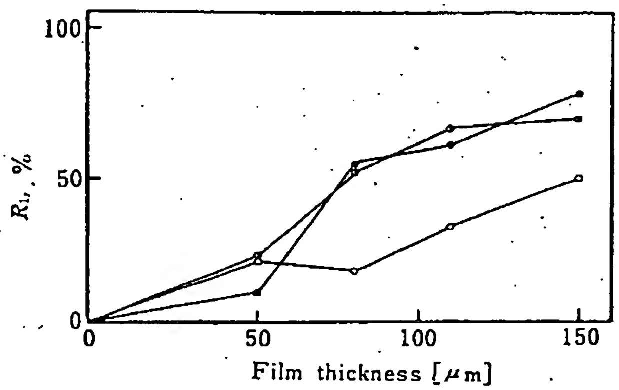

Fig. 11. Effect of Film Thickness on the Rate of Stabilization

●, first process; ◑, second process; ○, third process.

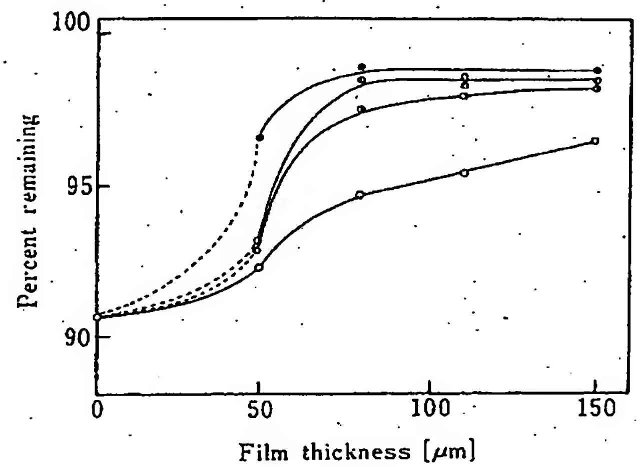

Fig. 12. Effect of Film Thickness on Percentage remaining in Photolytic Degradation

Concentration of opacificient:
○, 0%; ◑, 0.5%; ◐, 1.0%; ●, 1.5%.

In this plot, although the film thickness affects all the degradation processes, its effect seems to be most marked in the earliest process.

Since the spectrophotometric change was small even for the control (Fig. 9), it is difficult to follow this change precisely at short time intervals for films having lower average transmittance. Therefore, the photostability was evaluated in terms of the conversion after a long exposure time of 120 min. These conversion are plotted against thickness in Fig. 12 for every concentration of opacificient tested. In spite of the strong UV irradiation, conversions were below 3% at thicknesses above 80 μm at every concentration. Judging from the results in Fig. 12, the usual additive concentration of opacificient and film thickness used in commercially available capsules should give excellent protection of indomethacin.

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